AMENDMENTS TO THE DRAWINGS

The attached sheet of replacement drawing includes amended Figure 2. Figure 2 has been amended to change the "t" found in the string of nucleotides to "u." This change is supported in the description of Scheme1, as originally found on page 16 of the specification as filed which states that the scheme shows preproNPY mRNA. The "u" is present in mRNA, not "t" which is present in DNA.

Attachment: Replacement Sheet of Figure 2

REMARKS

The specification has been amended to insert sequence identifiers to the sequences found in Figures 2 and 3. The specification on page 8 has been amended to insert sequence identifiers for the sequences found on page 8 and to correct the sequence of the mutated form of the preproNPY mRNA. The sequence of the mutated form of preproNPY is shown in Figure 1b and 1c. Thus, page 8 has been amended to conform to the mutated sequence shown in the Figures.

Claims 4-7 and 11 have been canceled as being drawn to non-elected inventions without prejudice to filing one or more division applications.

Claim 8 has been amended to clarify the language concerning the polymorphism, to indicate that the oligonucleotide is an antisense oligonucleotide and to specify that this antisense oligonucleotide is complementary to the sequence 5'-acaagcgaccgg-3' (SEQ ID NO:9) and includes a base complementary to the "c" at position 10 of SEQ ID NO:9. Support for these amendments can be found at page 7, line 12 - page 8, line 8 of the specification.

Claim 14 has been amended to antisense oligonucleotide comprises 7 or 8 bases. Support for this amendment can be found at page 7, line 12 - page 8, line 8 of the specification.

Claim 15 has been canceled in view of the amendment to claim 8.

New claim 16 has been added to claim an antisense oligonucleotide that is fully complementary to the specified sequence. Support for this claim can be found at page 8, lines 1-8 of the specification.

Figure 2 has been corrected to set forth the proper nucleotide "u" in place of "t" in the string of nucleotides in view of the fact that the figure shows the predicted secondary structure of mRNA.

It is submitted that none of the above amendments constitute new matter and their entry is requested.

The Examiner objected to the specification for failure to comply with the sequence rules. The specification has been amended to set forth sequence identifiers, and a substitute Sequence

Listing is attached. It is submitted that the amendment of the specification and submission of the substitute Sequence Listing brings the application into compliance with the sequence rules.

The Examiner has rejected claims 8 and 14-15 under 35 U.S.C. § 112, first paragraph for lack of written description. As part of the rejection, the Examiner contends that the specification does not teach the complete structure of any antisense nucleotide. As shown below, the Examiner is in error in this contention.

In response to this rejection, claim 15 has been canceled. Claim 8 has been amended to specify that the oligonucleotide is an antisense oligonucleotide that is complementary to the sequence 5'-acaagcgaccgg-3' (SEQ ID NO:9) and includes a base complementary to the "c" at position 10 of SEQ ID NO:9. Claim 14 has been amended to specify that the antisense oligonucleotide of claim 8 comprises 7 or 8 bases. Claim 16 has been added to claim an antisense oligonucleotide having fully complementarity to the specified sequence.

The specification discloses that the present invention is directed to antisense oligonucleotides (page 7, line 17 - page 8, line 8). These antisense oligonucleotides can be of various lengths (page 8, lines 3-4) including 7 or 8 bases in length (page 7, lines 25-26). The antisense oligonucleotides are complementary to the mRNA (page 7, lines 20-23). The antisense oligonucleotides recognize the mutated base sequence (page 8, lines 3-4). The best target sequence is between -9 and +2 bases around the mutation (page 8, lines 5-6). Thus, according to the specification, the antisense oligonucleotides are targeted to (i.e., complementary to) the sequence 5'-acaagcgaccgg-3' (SEQ ID NO:9) (page 8, lines 5-7) and are targeted around the mutation (page 8, lines 3-4). Thus, it is submitted that the specification provides a written description of the claimed invention.

In view of the above amendments and remarks, it is submitted that the claims comply with the written description requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is requested.

The Examiner has rejected claims 8 and 14-15 under 35 U.S.C. § 112, first paragraph for lack of enablement. It is submitted that the presently claimed subject matter as set forth in amended claims 8 and 14 and in new claim 16 is fully enabled by the specification.

As noted above, claim 15 has been canceled. Claims 8, 14 and 16 are directed to antisense oligonucleotides that are complementary to the sequence 5'-acaagcgaccgg-3' (SEQ ID NO:9) and includes a base complementary to the mutated base "c" at position 10 of SEQ ID NO:9.

The Examiner has cited Lebedeva et al. (Levedeva, I. and Stein, C.A. (2001). "Antisense Oligonucleotides: Promise and reality." *Ann Rev Pharmacol Toxicol* 41:403-419) to support his contention that the claimed invention is not enabled. A careful review of Lebedeva et al. demonstrates that this article does not support the rejection. Although Lebedeva et al. does describe difficulties associated with antisense therapy in the context of specific therapies, such as the passages cited by the Examiner, it also describes techniques that have been used to overcome such difficulties. For example, although Lebedeva et al. disclose problems with phosphodiester oligonucleotides and others, it discloses solutions to these problems. See pages 404-408.

Similarly, although Lebedeva et al. discusses problems with irrelevant cleavage by RNase H, it discloses that these problems can be reduced by using shorter olignoculeotides. Applicants note that claim 14 is directed to an antisense oligonucleotides comprising 7 or 8 bases and claim 16 is directed to an antisense oligonucleotide of 12 bases. Other techniques have been shown by Lebedeva et al. to reduce irrelevant cleavage by RNase H. See page 410.

Furthermore, the difficulty of delivery of the antisense oligonucleotides, such as discussed for bcl-2 antisense therapy in Lebedeva et al., was overcome in studies also cited by Lebedeva et al. at pages 411-412. Finally, Applicants note that not only does Lebedeva et al. disclose that bcl-2 antisense therapy has therapeutic potential as a combined therapy, it also discloses that bcl-2 antisense therapy has therapeutic potential alone ("both **as a single agent** and in combination; page 414, emphasis added). Thus, Applicants submit that Lebedeva et al. demonstrate the high level in

the art for developing antisense oligonucleotides that circumvent the problems that have arisen in antisense therapy.

The Examiner also cites Lebedeva et al. for the fact that the selection of antisense oligonucleotide sequences may be expensive and laborious. However, as the Examiner is well aware, the fact that something may be laborious does not mean that undue experimentation is involved. In fact, in the present application, it is submitted that selection of the claimed antisense oligonucleotide is not laborious. Applicants have disclosed a specific sequence to which the antisense oligonucleotide should be targeted, i.e., 5'-acaagcgaccgg-3' (SEQ ID NO:9). Applicants have shown that this mutant sequence contains bulbs within the mRNA. See Figure 3 in comparison to Figure 2. A skilled artisan recognizes that bulbs enhance the binding of antisense oligonucleotides to mRNA. Thus, it is submitted that Applicants have fully disclosed the target sequence to which the antisense oligonucleotide is targeted and no laborious selection of antisense oligonucleotides is necessary.

Finally, the Examiner contends that no antisense therapy for diabetic retinophathy has been published. However, the Examiner's attention is directed to U.S. published patent application number 2004/0006004 A1, a copy of which is attached for the convenience of the Examiner. This published application demonstrates that an antisense oligonucleotide directed to the NPY Y2 receptor mRNA is effective *in vivo* for treating retinopaphy in rats. See especially paragraphs [0005] and [0063] and Figure 3 of the published application. This published application demonstrates that retinopathies can be treated by antisense therapy, i.e., that enough nucleic acid can reach the target site in sufficient amounts for sufficient length of time to yield a therapeutic effect. Applicants further note that Lebedeva et al. shows these same features for bcl-2 antisense therapy.

In view of the above amendments and remarks, it is submitted that the claims comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is requested.

In view of the above amendments and remarks, it is submitted that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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Attachments: Replacement Figure 2
Substitute Sequence Listing
Notice to Comply
U.S. published patent application No. 2004/0006004 A1

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